MCHIR ANTAGONISTS

Field of invention

The present invention relates to certain *N*-cycloalkyl, aryl or heteroaryl *N'*-quinolin-2-yl alkyldiamines of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

Melanin concentrating hormone (MCH) is a cyclic peptide that was first isolated from fish over 15 years ago. In mammals, MCH gene expression is localised to the ventral aspect of the zona inserta and the lateral hypothalamic area (Breton et al., Molecular and Cellular Neurosciences, vol. 4, 271-284 (1993)). The latter region of the brain is associated with the control of behaviours such as eating and drinking, with arousal and with motor activity (Baker, B., Trends Endocrinol. Metab. 5: 120-126(1994), vol. 5, No. 3, 120-126 (1994)). Although the biological activity in mammals has not been fully defined, recent work has indicated that MCH promotes eating and weight gain (US 5,849,708). Thus, MCH and its agonists have been proposed as treatments for anorexia nervosa and weight loss due to AIDS, renal disease, or chemotherapy. Similarly, antagonists of MCH can be used as a treatment for obesity and other disorders characterised by compulsive eating and excessive body weight. MCH projections are found throughout the brain, including the spinal cord, an area important in processing nociception, indicates that agents acting through MCH1r, such as compounds of formula I, will be useful in treating pain.

Two receptors for MCH (MCH1r (Shimomura et al. Biochem Biophys Res Commun 1999 Aug 11;261(3):622-6) & MCH2r (Hilol et al. J Biol Chem. 2001 Jun 8;276(23):20125-9)) have been identified in humans, while only one (MCH1r) is present in rodent species (Tan et al. Genomics. 2002 Jun;79(6):785-92). In mice lacking MCH1r, there is no increased feeding response to MCH, and a lean phenotype is seen, suggesting that this receptor is

responsible for mediating the feeding effect of MCH (Marsh et al. Proc Natl Acad Sci U S A. 2002 Mar 5;99(5):3240-5). In addition, MCH receptor antagonists have been demonstrated to block the feeding effects of MCH (Takekawa et al. Eur J Pharmacol. 2002 Mar 8;438(3):129-35), and to reduce body weight & adiposity in diet-induced obese rats (Borowsky et al. Nat Med. 2002 Aug;8(8):825-30). The conservation of distribution and sequence of MCH1r suggest a similar role for this receptor in man and rodent species. Hence, MCH receptor antagonists have been proposed as a treatment for obesity and other disorders characterised by excessive eating and body weight.

US 3,020,283 discloses that certain *N,N'*- bis lepid-2-yl 1,x-diamino C_{1-x} alkanes where x is an integer from 2 to 12 and *N,N'*- bis lepid-2-yldiaminocycloalkanes are useful as anthelmintics.

US 5,093,333 discloses certain *N*- substituted (cyclicaminoalkyl) 2-aminoquinolines which are useful for treating hypofunction of the cholinergic system and therefore useful in treating dementias involving the cholinergic system.

US 4,203,988 discloses certain pyridinyl and quinolinyl ureas which are useful in treating gastric secretion.

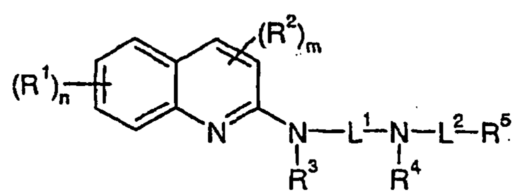
WO99/55677 discloses 2-(aminoalkylamino)quinolin-4-ones which are useful as anti-bacterial agents.

WO02/58702 discloses substituted 2-(aminoalkyl amino) quinolines which are antagonists of urotensin II which are alleged to be useful in treating cardiovascular diseases characterised by excessive or abnormal vasoconstriction and myocardial dysfunction and also in diseases of the CNS for example addiction, schizophrenia, anxiety and depression and metabolic diseases such as diabetes.

The present invention provides compounds that are MCH1r antagonists which are useful in treating obesity and related disorders, psychiatric disorders, neurological disorders and pain.

Description of the invention

The invention relates to compounds of the general formula (I)



I

wherein

R^1 represents a C_{1-4}alkoxy group optionally substituted by one or more fluoro or a C_{1-4}alkyl group optionally substituted by one or more fluoro;

n represents 0 or 1;

R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro ;

m represents 0 or 1;

R^3 represents H or a C_{1-4}alkyl group;

L^1 represents an alkylene chain $(CH_2)_r$ in which r represents 2 or 3 or L^1 represents a cyclohexyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclohexyl group either via the 1,3 or the 1,4 positions of the cyclohexyl group or L^1 represents a cyclopentyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclopentyl group via the 1,3 position of the cyclopentyl group and

additionally when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl the group $-L^1-N(R^4)-$ together represents a piperidyl ring which is linked to L^2 through the piperidinyl nitrogen and to N-R^3 via the 4 position of the piperidyl ring with the proviso that when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl then r is only 2;

R^4 represents H or a C_{1-4}alkyl group optionally substituted by one or more of the following: an aryl group or a heteroaryl group;

L^2 represents a bond or an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: a C_{1-4}alkyl group, phenyl or heteroaryl;

R^5 represents aryl, a heterocyclic group or a C_{3-8}cycloalkyl group which is optionally fused to a phenyl or to a heteroaryl group;

as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof;

with a first proviso that when n is 0, and m is 1 and R^2 is methyl located at the 4-position of the quinoline ring, and R^3 is H and R^4 is H and L^1 is $(CH_2)_2$ or $(CH_2)_3$ or 1,4-cyclohexyl, and L^2 is a bond then R^5 is not 4-methylquinolin-2-yl;

and with a second proviso that when n is 0, and m is 0 or 1 and R^2 is a C_{1-3}alkoxy group located at the 4-position of the quinoline ring, and R^3 is H or a C_{1-3}alkyl group and R^4 is H or a C_{1-3}alkyl group and L^1 is $(CH_2)_3$ and L^2 is methylene optionally substituted by one or more C_{1-3}alkyl groups or phenyl then R^5 is not phenyl, thienyl or indolyl optionally substituted by one, two or three C_{1-4}alkyl groups or halo.

The term "aryl" as used herein means phenyl, naphthyl, or 9, 10-methanoanthracen-9(10*H*)-yl, each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group, phenyl, or a group of formula NR^6R^7 wherein R^6 and R^7 are independently selected from H or a C_{1-4}alkyl group.

The term "heteroaryl" as used herein means thienyl, furyl or pyrrolyl.

The term "heterocyclic group" as used herein means thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl or benzo[*b*]thienyl each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group, a C_{1-4}acyl group or nitro. In one group of compounds the term "heterocyclic group" means thienyl, furyl, pyrrolyl, quinolinyl, indolyl or benzo[*b*]thienyl each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group, a C_{1-4}acyl group or nitro.

In one group of compounds of formula (I) : R^1 represents a C_{1-4}alkoxy group; n represents 0 or 1; R^2 represents a C_{1-4}alkyl group; m represents 0 or 1; R^3 represents H or a C_{1-4}alkyl group; L^1 represents an alkylene chain $(CH_2)_r$ in which r represents 2 or 3 with the proviso that r is only 2 when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl, or L^1 represents a cyclohexyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclohexyl group either via the 1,3 or the 1,4 positions of the cyclohexyl group and additionally when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl the group $-L^1-N(R^4)-$ together represents a piperidyl ring which is linked to L^2 through the piperidinyl nitrogen and to $N-R^3$ via the 4 position of the piperidyl ring; R^4 represents H or a C_{1-4}alkyl group optionally substituted by one or more of the following: an aryl group or a heteroaryl group; L^2 is represents a bond or an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: a C_{1-4}alkyl group, phenyl or heteroaryl; R^5 represents aryl, a heterocyclic group or a C_{3-8}cycloalkyl group which is optionally fused to a phenyl or to a heteroaryl group; as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

Further particular values of R^1, R^2, R^3, R^4, R^5, L^1, L^2, n, m, r and s in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Particularly R^1 represents a C_{1-4}alkoxy group. More particularly R^1 represents methoxy. Most particularly R^1 represents 6-methoxy when n is 1.
Particularly n represents 1.

Particularly R^2 represents a C_{1-4}alkyl group. More particularly R^2 represents methyl. Most particularly R^2 represents 4-methyl when m is 1.
Particularly m represents 1.

Particularly L^1 represents trimethylene, 1,3-cyclopentyl, 1,3-cyclohexyl or 1,4-cyclohexyl or when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl L^1 additionally represents ethylene. In one group of compounds of formula I, L^1 represents trimethylene. In a second group of compounds of formula I, L^1 represents 1,3-cyclohexyl. In a third group of compounds of formula I, L^1 represents 1,4-cyclohexyl. In a fourth group of compounds of formula I, L^1 represents 1,3-cyclopentyl.

In a particular group of compounds the group $-L^1-N(R^4)-$ together represents a piperidyl ring which is linked to L^2 through the piperidinyl nitrogen and to $N-R^3$ via the 4 position of the piperidyl ring with the proviso that R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl.

Particularly R^3 represents H or a C_{1-4}alkyl group especially methyl. In a particular group of compounds of formula I, R^3 represents H.

Particularly L^2 represents a bond, methylene, methylmethylene, dimethylene optionally substituted by phenyl, or trimethylene optionally substituted by methyl. In a particular group of compounds of formula I, L^2 is methylene.

Particularly R^4 represents H or a C_{1-4}alkyl group optionally substituted by a heteroaryl group. More particularly R^4 represents H, a C_{1-4}alkyl group or thienylmethyl. In a particular group of compounds of formula I, R^4 represents H.

Particularly R^5 represents phenyl, 2-naphthyl or 9, 10-methanoanthracen-9(10*H*)-yl, each of which is optionally substituted by one or more of the following: methyl, chloro, dimethylamino or phenyl.

More particularly R^5 represents 4, 5, 6, 7-tetrahydrothianaphth-4-yl , benzo[*b*]thien-3-yl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, benzofuranyl, pyridyl, 1*H*-pyrrol-2-yl, 1*H*-indol-3-yl, or 2-quinolinyl, each of which is optionally substituted by one or more of the following: nitro, methyl, acetyl or chloro.

Most particularly R^5 represents cyclopropyl, phenyl, 2, 4, 6-trimethylphenyl, 3, 4-dichlorophenyl, 2-naphthyl, 9, 10-methanoanthracen-9(10*H*)-yl, 2-thienyl, 3-thienyl, 5-nitro-3-thienyl, 2,5-dimethyl-3-thienyl, 3-furanyl, 5-methyl-2-furanyl, 1-acetyl-1*H*-indol-3-yl, 4, 5, 6, 7-tetrahydrothianaphth-4-yl , benzo[*b*]thien-3-yl, 1*H*-indol-3-yl, 2-quinolinyl, 1, 1'-biphenyl-4-yl, 4-(dimethylamino)phenyl, 1*H*-pyrrol-2-yl or 2,5-dichloro-3-thienyl.

The term "pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula **I** is, for example, an acid-addition salt of a compound of Formula **I** which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt,or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be separated using

conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

The present invention provides a compound selected from:
N-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)-*N*′-(2-quinolinyl)-1, 2-ethanediamine;
N-(6-methoxy-4-methyl-2-quinolinyl)-*N*′-(3-thienylmethyl)-1, 3-propanediamine;
N-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;
N-(2-quinolinyl)-*N*′-(3-thienylmethyl)-1, 3-propanediamine;
N-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)-*N*′-(2-quinolinyl)-1, 4-cyclohexanediamine;
N-[(1-acetyl-1*H*-indol-3-yl)methyl]-*N*′-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine;

N-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)- *N*′-(2-quinolinyl)-1, 3-cyclohexanediamine;

N-(2-quinolinyl)-*N*′-[1-(3-thienyl)ethyl]-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′-(3-thienylmethyl)-1, 3-cyclohexanediamine;

N-(9,10-methanoanthracen-9(10*H*)-ylmethyl)-*N*′-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′-(4, 5, 6, 7-tetrahydrothianaphth-4-yl)-1, 3-propanediamine;

N-methyl-*N*′-(2-quinolinyl)-*N*-(3-thienylmethyl)-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′, *N*′-bis(3-thienylmethyl)-1, 3-propanediamine;

N- (9, 10-methanoanthracen-9(10*H*)-ylmethyl)-*N*-methyl-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′-[(2, 4, 6-trimethylphenyl)methyl]-1, 3-propanediamine;

N-(2-phenylethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(1-benzo[*b*]thien-3-ylethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-[(3, 4-dichlorophenyl)methyl]-*N*′-(2-quinolinyl)-1, 3-cyclohexanediamine;

N-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)-*N*′-methyl-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′-(2-thienylmethyl)-1, 3-propanediamine;

N-(3-furanylmethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-[(3, 4-dichlorophenyl)methyl]-*N*-methyl-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-[1-(9, 10-methanoanthracen-9(10*H*)-ylmethyl)-4-piperidinyl]-2-quinolinamine;

N-(1*H*-indol-3-ylmethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(2-naphthalenylmethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(2, 2-diphenylethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(1*H*-indol-3-ylmethyl)-*N*′-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine;

N-[(3, 4-dichlorophenyl)methyl-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-[(3, 4-dichlorophenyl)methyl]-*N*′-(2-quinolinyl)-1, 4-cyclohexanediamine;

N, *N*′-di-(2-quinolinyl)-1 ,3-propanediamine;

N-(2-quinolinyl)-*N*′-(2-quinolinylmethyl)-1, 3-propanediamine;

N-[(1-acetyl-1*H*-indol-3-yl)methyl]-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(cyclopropylmethyl)-*N*′-(2-quinolinyl)-1, 3-propanediamine;

N-(2-quinolinyl)-*N*′-(3-thienylmethyl)-1, 4-cyclohexanediamine;

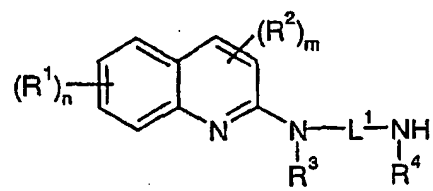
N-([1, 1'-biphenyl]-4-ylmethyl)-*N'*-(2-quinolinyl)-1, 3-propanediamine;
N-(6-methoxy-4-methyl-2-quinolinyl)-*N'*-[3-(5-methyl-2-furanyl)butyl]-1, 3-propanediamine;
N-[[4-(dimethylamino)phenyl]methyl]-*N'*-(2-quinolinyl)-1, 3-propanediamine;
N-(1*H*-pyrrol-2-ylmethyl)-*N'*-(2-quinolinyl)-1, 3-propanediamine;
N-[3-(5-methyl-2-furanyl)butyl]-*N'*-(2-quinolinyl)-1, 3-propanediamine;
N-[(5-nitro-3-thienyl)methyl]-*N'*-(2-quinolinyl)-1, 3-propanediamine;
N-(6-methoxy-4-methyl-2-quinolinyl)-*N'*-[(5-nitro-3-thienyl)methyl]-1, 3-propanediamine;
N-(6-methoxy-4-methyl-2-quinolinyl)-*N'*-(1*H*-pyrrol-2-ylmethyl)-1, 3-propanediamine;
N-[(3,4-dichlorophenyl)methyl]-*N'*-methyl-*N'*-2-quinolinyl)-1, 3-propanediamine;
N-[1-(2,5-dimethyl-3-thienyl)ethyl]-*N'*-(2-quinolinyl)-1,3-propanediamine;
N-[1-(2,5-Dichloro-thiophen-3-yl)-ethyl]-*N'*-(2-quinolinyl)-1,3-propanediamine;
N-[(1-acetyl-1*H*-indol-3-yl)methyl]-*N'*-quinolin-2-ylcyclohexane-1,3-diamine;
N-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclopentane-1,3-diamine;*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine;
(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine
(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclopentane-1,3-diamine
N-[(1-acetyl-1*H*-indol-3-yl)methyl]-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine;
N-(1*H*-indol-3-ylmethyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine;
N-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine;
N-(6-methoxy-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclohexane-1,3-diamine;
N-(1-benzofuran-2-ylmethyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine; *N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(pyridin-2-ylmethyl)cyclohexane-1,3-diamine and
N-(4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine;

as well as pharmaceutically acceptable salts thereof.

Methods of preparation

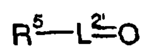
The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I may be prepared by reacting a compound of formula II



II

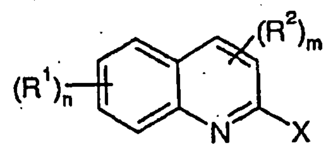
in which R^1, R^2, R^3, R^4, L^1, n and m are as previously defined with a compound of formula III



III

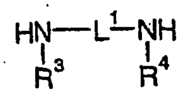
in which R^5 is as previously defined and $L^{2'}$ represents a group which after reaction of compounds II and III gives L^2 on reduction, under reductive alkylation conditions. For example, a compound of formula II and a compound of formula III may be reacted together at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to 150°C, optionally in the presence of an inert solvent, for example methanol, dichloromethane or acetic acid in the presence of a reducing agent for example (polystyrylmethyl)trimethyl-ammonium cyanoborohydride or sodium cyanoborohydride which is optionally polymer supported.

Compounds of formula II may be prepared by reacting a compound of formula IV



IV

in which R^1, R^2, n and m are as previously defined and X is halo, particularly chloro or bromo, with a compound of formula V



V

at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to 150°C,optionally in the presence of an inert solvent, for example toluene, optionally in the presence of a catalytic cross-coupling system for example $Pd(OAc)_2$ and 2-(di-^{t}butylphosphino)biphenyl or BINAP, and optionally in the presence of a base for example NaO^tBu.

Certain compounds of formula II are novel and are claimed as a further aspect of the present invention as useful intermediates.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction). Optionally a nitrogen in formula V may be protected prior to reaction with a compound of formula IV and then the compound of formula II obtained is deprotected prior to reaction with a compound of formula III. Amine protecting groups are known to those skilled in the art for example the t-BOC group.

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutically acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with obesity, psychiatric disorders, neurological disorders and pain.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Raynaud's syndrome , Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems. The compounds are also potentially useful as agents for ceasing consumption of tobacco, treating nicotine dependence and/or treating nicotine withdrawal symptoms, reducing the craving for nicotine and as anti-smoking agents. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking. The compounds are also potentially useful as agents for treating or preventing diarrhoea.

The compounds are also potentially useful as agents for reducing the craving/relapse for addictive substances that include, but are not limited to psychomotor-active agents such as nicotine, alcohol, cocaine, amphetamines, opiates, benzodiazepines and barbiturates. The compounds are also potentially useful as agents for treating drug addiction and/or drug abuse.

Accordingly, it is desirable to provide a compound and method of treatment which will be

active in reducing craving for the abused substance, and which does not exacerbate the sympathetic response rate caused by the abused substance and which has favorable pharmacodynamic effects.

The compounds are also potentially useful as agents for treating pain disorders , including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders , including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to

in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist ;

another Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically

acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Working examples

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

Abbreviations

aq.	aqueous
Ac	acetyl
BINAP	*rac*-2,2'-Bis(diphenyl-phosphino)-1,1'-binaphtyl
Bu	butyl
DMF	*N, N'*-dimethylformamide
EtOAc	ethyl acetate
Et_2O	diethyl ether
HEK	human embryotic kidney
HOAc	acetic acid

HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectroscopy
MeOH	methanol
Pol-BH_3CN	(polystyrylmethyl)trimethylammonium cyanoborohydride
Pol-CHO	4-benzyloxybenzaldehyde polystyrene
TFA	trifluoroacetic acid
THF	tetrahydrofuran
MeCN	acetonitrile
NEt_3	triethylamine
Tris	trishydroxymethylaminomethane
t	tert
rt.	room temperature
sat.	saturated
br	broad
bs	broad singlet
bt	broad triplet
d	doublet
dd	doublet of doublets
m	multiplet
q	quartet
s	singlet
t	triplet
tt	triplet of triplets
td	triplet of doublets
bd	broad doublet

General Experimental Procedures

Flash column chromatography employed Matrex normal phase silica gel 60 Å (30-70) µM. Mass spectra were recorded on a Micromass ZQ single quadrupole equipped with a pneumatically assisted electrospray interface (LC-MS). Purifications were performed on either a semi preparative HPLC with a mass triggered fraction collector, Shimadzu QP

8000, equipped with a XTerra 100 mm x 19 mm C18 5 μm column, or on a Waters FractionLynx HPLC with a mass triggered fraction collector, equipped with a Ace μm 5 5μm C8 100 mm x 21.2 mm column or on a Waters Prep LC 2000 with UV-detection, equipped with a Kromasil 10 μm C8 250 mm x 20 mm column, or on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® 100 mm x 19 mm C18 5 μm column. ^{1}H NMR and ^{13}C NMR spectra were obtained at 298 K on a Varian Unity Plus 400 mHz, or a Varian INOVA 500 MHz or Bruker Avance 300 MHz. Chemical shifts are given in ppm with the solvent residual peak as internal standard: $CDCl_3$ δ_H 7.26, δ_C 77.2; MeOH-d_4 δ_H 3.31, δ_C 49.0; DMSO-d_6 δ_H 2.50; δ_C 39.5 ppm, DMF-d_7 δ_H 2.75/2.95/8.05, acetone-d_6 δ_H 2.05, THF-d_8 δ_H 1.74/3.60 ppm.. Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden.

__*Synthesis of Starting Materials and Intermediates*__

A1 *N*-Quinolin-2-ylpropane-1,3-diamine

A mixture of 2-chloroquinoline (4.80 mmol, 1.0 g), 1, 3-propanediamine (7.20 mmol, 0.534 g), NaO^{t}Bu (6.72 mmol, 0.646 g), $Pd(OAc)_2$ (0.048 mmol, 0.011 g), and 2-(di-^{t}butylphosphino)biphenyl (0.048 mmol, 0.014 g) in toluene (12 mL) was stirred at 100 °C under nitrogen until LC-MS indicated that starting material was consumed. The reaction mixture was cooled to room temperature, poured into Et_2O (100 mL) and filtered through a plug of filtration aid. The filtrate was concentrated and the residue purified on a pre-packed SiO_2 column (70 g) eluted with CH_2Cl_2 (containing 0.5% HOAc, 300 mL), CH_2Cl_2:MeOH (5:1, 300 mL), and finally with CH_2Cl_2:MeOH:H_2O (10:6:1, containing 1% Et_3N) to give 0.915 g (95%) of the title compound. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.85 (d, J = 10.1 Hz, 1H), 7.62 - 7.58 (m, 2H), 7.51 (t, J = 8.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 2H), 6.76 (d, J = 8.8 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 2.92 (t, J = 6.6 Hz, 2H), 1.93 (quintet, J = 6.8 Hz, 2H).

A2 *N*-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine

The title compound was prepared from 2-chloro-6-methoxy-4-methylquinoline and 1, 3-propanediamine using the procedure described for preparation A1. Yield quantitative. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.42 (d, J = 9.1 Hz, 1H), 7.12 - 7.078 (m, 2H), 6.57 (s, 1H), 3.80 (s, 3H), 3.37 (t, J = 6.6 Hz, 2H), 2.66 (bt, J = 6.6 Hz, 2H), 2.43 (s, 3H), 1.67 (quintet, J = 6.8 Hz, 2H).

A3 *N*-Quinolin-2-ylcyclohexane-1, 4-diamine

The title compound was prepared as a mixture of isomers from 2-chloroquinoline and cyclohexane-1, 4-diamine using the procedure described for preparation A1. Yield 94%. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.92 (d, J = 9.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 4.17 - 4.09 (m, 1H), 3.29 - 3.21 (m, 1H), 2.22 - 2.08 (m, 1H), 1.94 - 1.75 (m, 6H), 1.69 - 1.37 (m, 1H).

A4 *N*-Quinolin-2-ylcyclohexane-1, 3-diamine

The title compound was prepared as a mixture of diastereomers from 2-chloroquinoline and cyclohexane-1, 3 -diamine using the procedure described for preparation A1. Yield 84%. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.82 (d, J = 8.9 Hz, 1H), 7.61 - 7.57 (m, 2H), 7.48 (t, J = 8.5 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 9.1 Hz, 1H), 4.12 - 4.04 (m, 1H), 3.28 - 3.21 (m, 2H), 2.56 - 2.50 (m, 1H), 2.07 (t, J = 12.0 Hz, 1H), 1.98 - 1.93 (m, 1H), 1.82 - 1.75 (m, 1H), 1.62 - 1.49 (m, 1H), 1.41 - 1.23 (m, 2H).

A5 *N*-Quinolin-2-ylethane-1, 2-diamine

The title compound was prepared from 2-chloroquinoline and 1, 2-ethanediamine using the procedure described for preparation of A1. Yield 65%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.81 (d, J = 9.1 Hz, 1H), 7.61 - 7.56 (m, 2H), 7.47 (t, J = 8.5 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 3.55 (t, J = 6.2 Hz, 2H), 2.91 (t, J = 6.1 Hz, 2H).

A6 *N*-Methyl-*N*´-quinolin-2-ylpropane-1, 3-diamine

The title compound was prepared from 2-chloroquinoline and *N*'-methyl-1, 3-propanediamine using the procedure described for preparation A1. Yield 61%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.87 (d, J = 9.06 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.56 – 7.50 (m, 1H), 7.22 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.9Hz, 1H), 3.63 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 6.5 Hz, 2H), 2.65 (s, 3H), 2.02 (m, 2H).

A7 *N*-Methyl-*N*-quinolin-2-ylpropane-1, 3-diamine

The title compound was isolated from preparation A6. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.03 (d, J = 9.1 Hz, 1H), 7.69 – 7.59 (m, 2H), 7.58 – 7.52 (m, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 9.1 Hz, 1H), 3.88 (t, J = 6.2 Hz, 2H), 3.16 (s, 3H), 2.94 (t, J = 6.4 Hz, 2H), 2.02 (m, 2H).

A8 *N*-Piperidin-4-ylquinolin-2-amine

The title compound was prepared from 2-chloroquinoline and piperidin-4-ylamine using the procedure described for preparation A1. Yield 18%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.77 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 8.5 Hz, 1H), 7.21 - 7.07 (m, 1H), 6.71 (d, J = 9.8 Hz, 1H), 4.13 - 4.06 (m, 1H), 3.13 (d, J = 12.5 Hz, 2H), 2.80 (dt, J = 3.1, 13.7 Hz, 2H), 2.10 - 2.06 (m, 2H), 1.56 - 1.46 (m, 2H).

A9 9-Formyl-9,10-dihydro-9,10-methanoanthracene

Prepared according to literature preparation: H. Sunagawa, et al; Chem. Pharm. Bull. Vol. 27 (1979) pp 1806-1812; U.S. Pat. No. 4,224,344 Sunagawa et al, Sumitomo, Ltd.; Sep. 23, 1980; U.S. Pat. No. 4,358,620 Sunagawa et al, Sumitomo, Ltd.; Nov. 9, 1982.

A10 (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclopentyl methanesulfonate

Prepared according to literature preparation from (–)-2-azabicyclo[2.2.1]hept-5-en-3-one (>95% ee): H. Bergstrand, et al; Astra AB; New Pharmaceutically Active Compounds; WO9811103; Mars 19, 1998.

A11 *tert*-butyl [(1*S*,3*S*)-3-azidocyclopentyl]carbamate

NaN_3 (16.6 g, 0.25 mmol) was added to a stirred solution of (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclopentyl methanesulfonate (20 g, crude, ~0.05 mol) in DMF (250 mL) under nitrogen atmosphere. The mixture was heated to 50 °C for 18 h (over night). The mixture was allowed to reach rt. and poured into H_2O (200 mL) and extracted with EtOAc (2 × 400 mL), 200 mL Et_2O and concentrated. Purification of the residue by flash chromatography [280 g silica gel, 6 × 22 cm column, with EtOAc/heptane (2:3 → 1:1) as eluent] afforded the title compound (16.5 g, contaminated with DMF) as a slightly

yellowish oil taken to the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 4.52 (bs , 1H), 4.00–4.10 (m, 2H), 1.98–2.22 (m, 3H), 1.62–1.78 (m, 2H), 1.42–1.52 (m, 1H), 1.44 (s, 9 H).

A12 tert-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate

A flask containing *tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate (16.5 g, crude ~0.05 mol) from A11 and 1.7 g Pd-C (10% paste) in MeOH (300 mL) was exposed to a positive pressure of hydrogen gas (balloon) over weekend. The catalyst was filtrated off and the mixture was concentrated to afford the title compound (9.5 g) as a thick colorless viscous oil. ^{1}H NMR (DMSO-d_6) δ 6,74 (bd , 1H), 3.86–3.92 (m, 1H), 3.28 (quintet, 1H), 1.73–1.98 (m, 2H), 1.43–1.59 (m, 2H), 1.22–1.41 (m, 1H), 1.36 (s, 9 H), 1.07–1.20 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 155.0, 77.2, 50.8, 50.0, 42.6, 34.2, 31.2, 28.3. LC-MS $[M+H]^+$ 201

A13 *N*-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine

A mixture of 2-chloro-6-methoxy-4-methylquinoline (1.20 mmol, 0.250 g), 1,3-cyclohexanediamine (3.61 mmol, 0.412 g), NaO^{t}Bu (1.70 mmol, 0.162 g), $Pd(OAc)_2$ (0.02 mmol, 0.004 g), and 2-(di-^{t}butylphosphino)biphenyl (0.034 mmol, 0.010 g) in toluene (5 mL) was stirred at 100 °C under argon for 24 h. The reaction mixture was cooled to room temperature, diluted with EtOAc/MeOH 5:1 containing 1% NEt_3 and loaded directly on a short (~2cm) silica column. Elution with EtOAc/MeOH 5:1 containing 1% NEt_3 gave 0.241 g (70%) of the title compound as a mixture of diastereomers (~6:1). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.52 (d, J = 9.1 Hz, 1H, major isomer), 7.52 (d, J = 9.1 Hz, 1H, minor isomer), 7.12 (dd, J = 9.1, 2.8 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.62 (bs, 1H, minor isomer), 6.53 (bs, 1H, major isomer), 4.27 (m, 1H, minor isomer), 3.88 (tt, J = 11.6, 3.8 Hz, 1H, major isomer), 3.80 (s, 3H), 3.02 (m, 1H, minor isomer), 2.76 (tt, J = 11.4, 3.8 Hz, 1H, major isomer), 2.44 (bs, 3H, minor isomer), 2.42 (bs, 3H, major isomer), 2.21 (m, 1H), 2.02-0.96 (m, 7H) ; ^{13}C NMR (101 MHz, MeOH-d_4, major isomer) δ 156.8, 155.9, 145.3, 144.1, 127.5, 125.1, 120.8, 114.2, 104.8, 55.9, 50.5, 49.6, 43.5, 35.8, 33.6, 24.3, 18.9; LC-MS $[M+H]^+$ 286.1.

A14 *N*-(4-methylquinolin-2-yl)cyclohexane-1,3-diamine

A solution of 2-chloro-4-methylquinoline (0.200 g, 1.13 mmol) and 1,3-diaminocyclohexane (0.51 g, 4.5 mmol) in 3 mL of pyridine was subjected to single node microwave heating (210°C for 1h). The reaction mixture was cooled to room temperature and evaporated. The crude product was flash chromatographed on silica gel and eluted with EtOAc/MeOH/Et_3N 50:50:1 to give 0.24 g (84%) of the title compound as a mixture of diastereomers (~2.7:1).

^{1}H NMR (300 MHz, MeOH-d_4) δ 7.7-7.8 (m, 1H), 7.58-7.63 (m, 1H), 7.45-7.55 (m, 1H), 7.18-7.25 (m, 1H), 6.70 (bs, 1H, minor isomer) 6.61 (bs, 1H, major isomer), 4.44 (m, 1H, minor isomer), 4.06 (m, 1H, major isomer), 2.48-2.55 (m, 3H plus 1H, major isomer), 2.32 (m, 1H, minor isomer), 1.2-2.1 (m, 8H).

Examples

Example 1

N-(9, 10-Methanoanthracen-9(10*H*)-ylmethyl)-N'-(quinolin-2-yl)-1, 2-ethanediamine

Pol-BH_3CN (150 mg, pre-swollen in CH_2Cl_2) was added to a solution of *N*-quinolin-2-ylethane-1, 2-diamine (0.299 mmol, 0.056 g) and 9-formyl-9,10-dihydro-9,10-methanoanthracene (0.225 mmol, 0.050 g) in MeOH:CH_2Cl_2 (1:1, containing 1% HOAc, 2.5 mL), and the resultant slurry was subjected to microwave heating single node 100 °C, 5 min. The resin was filtered off and washed with portions (1-2 mL) of CH_2Cl_2 and MeOH, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (5 mL), and Pol-CHO (140 mg) was added, and the slurry was stirred at room temperature for 60 min. The resin was filtered off and washed with portions (1-2 mL each) of CH_2Cl_2. The filtrate was concentrated, and the residue was purified on SiO_2 (EtOAc:MeOH 9:1) to give 0.078 g (88%) of the title compound. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.85 (d, J = 8.9 Hz, 1H), 7.56 (dd, J = 1.2, 9.0 Hz, 1H), 7.39 (dt, J = 1.4, 11.5 Hz, 1H), 7.22 (d, J = 7.3 Hz, 2H), 7.14 (dt, J = 1.2, 7.9 Hz, 1H), 7.12 - 7.06 (m, 3H), 6.86 (dt, J = 1.2, 7.5 Hz, 2H), 6.82 - 6.75 (m, 3H), 4.30 (s, 1H), 4.02 (s, 2H), 3.80 (t, J = 5.2 Hz, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.55 (s, 2H).

Examples 2 to 45 were performed using the procedure described in Example 1 by reacting an amine with an aldehyde as stated.

Example 2

N-(6-Methoxy-4-methyl-2-quinolinyl)-N´-(3-thienylmethyl)-1, 3-propanediamine

This compound was prepared from *N*-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and 3-thiophenecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 34% yield. ^{1}H NMR (400 MHz, DMF-d_7) δ 7.48 - 7.46 (m, 1H), 7.45 (d, J = 9.1 Hz, 1H), 7.32 - 7.31 (m, 1H), 7.17 (dd, J = 2.6, 13.5 Hz, 2H), 7.13 (t, J = 4.2 Hz, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.77 (s, 2H), 3.53 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.7 Hz, 2H), 2.49 (s, 3H), 1.82 (quintet, J = 6.7 Hz, 2H).

Example 3

N-(9, 10-Methanoanthracen-9(10*H*)-ylmethyl)-N´-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified on SiO_2 (CH_2Cl_2:MeOH 20:1 → 10:1, containing 1% HOAc) to give the title compound in 50% yield. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.85 (d, J = 8.9 Hz, 1H), 7.57 (dd, J = 1.4, 9.3 Hz, 1H), 7.36 - 7.32 (m, 5H), 7.31 - 7.22 (m, 5H), 7.14 (t, J = 8.0 Hz, 1H), 7.01 - 6.93 (m, 5H), 6.75 (d, J = 9.1 Hz, 1H), 4.43 (s, 1H), 4.21 (s, 2H), 3.70 (t, J = 6.4 Hz, 2H), 3.31 (t, J = 1.4 Hz, 2H), 2.65 (s, 2H), 2.23 (quintet, J = 6.5 Hz, 2H).

Example 4

N-(2-Quinolinyl)-N´-(3-thienylmethyl)-1, 3-propanediamine

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and 3-thiophene-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 74% yield. ^{1}H

NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.50 - 7.48 (m, 2H), 7.43 (t, J = 8.5 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.15 - 7.13 (m, 1H), 6.75 (d, J = 9.5 Hz, 1H), 4.23 (s, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.06 (t, J = 7.1 Hz, 2H), 2.05 (quintet, J = 6.4 Hz, 2H).

Example 5

N-(9, 10-Methanoanthracen-9(10*H*)-ylmethyl)-*N*′-(2-quinolinyl)-1, 4-cyclohexanediamine

This compound was prepared from *N*-quinolin-2-ylcyclohexane-1, 4-diamine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a diastereomeric mixture in 25% yield. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.78 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.46 (t, J = 8.5 Hz, 1H), 7.24 (d, J = 7.7 Hz, 2H), 7.16 - 7.12 (m, 3H), 6.97 - 6.89 (m, 4H), 6.79 (d, J = 8.9 Hz, 1H), 4.27 (s, 1H), 4.23 - 4.19 (m, 1H), 3.67 (s, 2H), 2.90 - 2.85 (m, 1H), 2.51 (d, J = 1.4 Hz, 2H), 1.94 - 1.85 (m, 4H), 1.82 - 1.67 (m, 4H).

Example 6

***N*-[(1-Acetyl-1*H*-indol-3-yl)methyl]-*N*′-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine**

This compound was prepared from *N*-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and 1-acetyl-3-indolecarboxaldehyde, and purified on SiO_2 (CH_2Cl_2:MeOH 40:1 → 2:1) to give the title compound in 36% yield. ^{1}H NMR (400 MHz, MeOH-d_4, major rotamer) δ 8.33 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.26 - 7.21 (m, 2H), 7.10 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 2.8, 11.9 Hz, 1H), 6.54 (s, 1H), 4.08 (s, 2H), 3.84 (s, 3H), 3.57 (t, J = 6.3 Hz, 2H), 2.97 (t, J = 6.6 Hz, 2H), 2.49 (s, 3H), 2.47 (d, J = 0.8 Hz, 3H), 2.01 - 1.94 (m, 2H).

Example 7

N-(9, 10-Methanoanthracen-9(10H)-ylmethyl)- N'-(2-quinolinyl)-1, 3-cyclohexanediamine

This compound was prepared from N-quinolin-2-ylcyclohexane-1, 3-diamine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a mixture of diastereomers in 60% yield. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.75 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 8.6, 1H), 7.46 (dt, 1.2, 7.4 Hz, 1H), 7.23 - 7.08 (m, 5H), 6.95 – 6.84 (m, 4H), 6.68 (d, J = 9.0 Hz, 1H), 4.23 (s, 1H), 4.15 – 4.05 (m, 1H), 3.65 (d, J = 2.6 Hz, 2H), 2.92 – 2.81 (m, 1H), 2.53 – 2.39 (m, 3H), 2.13 – 2.01 (m, 2H), 1.91 – 1.81 (m, 2H), 1.60 – 1.46 (m, 1H), 1.29 – 1.12 (m, 2H).

Example 8

N-(2-Quinolinyl)-N'-[1-(3-thienyl)ethyl]-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 3-acetylthiophene, but subjected to microwave heating single node 140 °C, 5 min., and purified on SiO_2 (CH_2Cl_2:MeOH 1:0 $\rightarrow$ 0:1) to give the title compound in 30% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.80 (d, J = 9.1 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.48 - 7.37 (m, 4H), 7.18 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 5.0 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 4.42 - 4.38 (m, 1H), 3.59 - 3.55 (m, 2H), 2.91 - 2.79 (m, 2H), 2.02 - 1.93 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H).

Example 9

N-(2-Quinolinyl)-N'-(3-thienylmethyl)-1, 3-cyclohexanediamine

This compound was prepared from N-quinolin-2-ylcyclohexane-1, 3-diamine and 3-thiophenecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a mixture of diastereomers in 33% yield. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ

7.81 (d, J = 8.9 Hz, 1H), 7.58 (t, J = 9.1 Hz, 2H), 7.50 - 7.46 (m, 3H), 7.20 - 7.15 (m, 2H), 6.71 (d, J = 8.9 Hz, 1H), 4.12 (s, 2H), 4.09 - 4.00 (m, 1H), 3.12 - 3.04 (m, 1H), 2.59 (d, J = 11.9 Hz, 1H), 2.15 (d, J = 12.7 Hz, 1H), 2.08 (d, J = 14.0 Hz, 1H), 1.98 - 1.93 (m, 1H), 1.79 (s, 1H), 1.57 - 1.45 (m, 1H), 1.37 - 1.21 (m, 2H).

Example 10

N-(9,10-Methanoanthracen-9(10H)-ylmethyl)-N'-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified using HPLC (95% 0.1 M ammoniumacetatebuffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 20% yield. ^{1}H NMR (400 MHz, DMF-d_7,) δ 7.36 - 7.31 (m, 5H), 7.20 (d, J = 2.8 Hz, 1H), 7.11 (dd, J = 11.9, 2.8 Hz, 1H), 6.97 (d, J = 3.0 Hz, 2H), 6.95 (d, J = 3.2 Hz, 2H), 6.65 (s, 1H), 4.40 (s, 1H), 4.01 (s, 2H), 3.88 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 3.25 - 3.21 (m, 2H), 2.61 (s, 2H), 2.49 (s, 3H), 2.14 - 2.08 (m, 2H).

Example 11

N-(2-Quinolinyl)-N'-(4, 5, 6, 7-tetrahydrothianaphth-4-yl)-1, 3-propanediamine (alternative name N-quinolin-2-yl-N'-(4,5,6,7-tetrahydro-1-benzothien-4-yl)propane-1,3-diamine)

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 4-keto-4, 5, 6, 7-tetrahydrothianaphthene, but subjected to microwave heating single node 120 °C, 15 min., and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 $\rightarrow$ 4:1) to give the title compound in 34% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.82 (d, J = 9.3 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 8.3 Hz, 1H), 7.22 (d, J = 5.7 Hz, 1H), 7.18 - 7.12 (m, 3H), 6.73 (d, J = 8.4 Hz, 1H), 4.19 (t, J = 5.9 Hz, 1H), 3.76 - 3.69 (m, 1H), 3.56 - 3.50 (m, 1H), 3.00 (t, J = 7.2 Hz,

2H), 2.71 - 2.64 (m, 1H), 2.54 - 2.47 (m, 1H), 2.09 - 1.94 (m, 3H), 1.87 - 1.78 (m, 1H), 1.75 - 1.65 (m, 1H), 1.64 - 1.56 (m, 1H).

Example 12

_N_-Methyl-_N'_-(2-quinolinyl)-_N_-(3-thienylmethyl)-1, 3-propanediamine

This compound was prepared from *N*-methyl-*N'*-quinolin-2-ylpropane-1, 3-diamine and 3-thiophenecarboxaldehyde, and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 → 4:1) to give the title compound in 24% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.80 (d, J = 8.8 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.46 (dt, J = 1.4, 8.0 Hz, 1H), 7.31 (dd, J = 2.8, 7.8 Hz, 1H), 7.22 (bs, 1H), 7.16 (dt, J = 1.2, 7.4 Hz, 1H), 7.06 (dd, J = 1.2.8, 4.7 Hz, 1H), 6.70 (d, J = 8.8Hz, 1H), 3.62 (s, 2H), 3.48 (t, J = 6.8 Hz, 2H), 2.54 (t, J = 7.3 Hz, 2H), 2.25 (s, 3H), 1.90 (quintet, J = 7.0 Hz, 2H).

Example 13

_N_-(2-Quinolinyl)-_N'_, _N'_-bis(3-thienylmethyl)-1, 3-propanediamine

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and 3-thiophenecarboxaldehyde, but subjected to microwave heating single node 110 °C, 5 min., and purified on SiO_2 (CH_3Cl:MeOH 10:1 → 2:1) to give the title compound in 30% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.82 (d, J = 8.8 Hz, 1H), 7.60 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.32 (m, 1H), 7.23 (bs, 2H), 7.19 (m, 2H), 7.10 (d, J = 4.2 Hz, 2H), 6.65 (d, J = 9.1 Hz, 1H), 3.65 (s, 4H), 3.49 (t, J = 6.6 Hz, 2H), 2.59 (t, J = 6.6 Hz, 2H), 1.91 (quintet, J = 7.0 Hz, 2H).

Example 14

N- (9, 10-Methanoanthracen-9(10*H*)-ylmethyl)-*N*-methyl-*N*´-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from *N*-methyl-*N*´-quinolin-2-ylpropane-1, 3-diamine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 → 4:1) to give the title compound in 11% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.71 (d, J = 8.8 Hz, 1H), 7.56 (t, J = 8.2 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.19 - 7.14 (m, 5H), 6.89 - 6.83 (m, 4H), 6.40 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 3.51 - 3.48 (m, 4H), 2.76 (t, J = 6.9 Hz, 2H), 2.56 (s, 2H), 2.43 (s, 3H), 1.96 - 1.89 (m, 2H).

Example 15

***N*-(2-Quinolinyl)-*N*´-[(2, 4, 6-trimethylphenyl)methyl]-1, 3-propanediamine**

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and 2, 4, 6-trimethyl-benzaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 27% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.87 (d, J = 9.0 Hz, 1H), 7.59 (dd, J = 9.3, 1.6 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.18 - 7.14 (m, 1H), 6.96 (s, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 4.30 (s, 2H), 3.71 (t, J = 6.2 Hz, 2H), 3.21 (t, J = 6.7 Hz, 2H), 2.39 (s, 6H), 2.31 (s, 3H), 2.16 (quintet, J = 6.5 Hz, 2H).

Example 16

***N*-(2-Phenylethyl)-*N*´-(2-quinolinyl)-1, 3-propanediamine**

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and phenyl acetaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 4% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.88 (d, J = 9.0 Hz, 1H), 7.65 - 7.52 (m, 3H), 7.30 - 7.19 (m, 4H), 7.15 (d, J = 1.7 Hz, 1H), 7.13 (s, 1H), 6.77 (d, J = 9.1 Hz, 1H), 3.65 (t, J = 6.3 Hz, 2H), 3.22 - 3.18 (m, 2H), 3.11 (t, J = 6.8 Hz, 2H), 2.95 - 2.91 (m, 2H), 2.04 (quintet, J = 6.5 Hz, 2H).

Example 17

N-(1-Benzo[*b*]thien-3-ylethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 3-acetylthianaphthene but subjected to microwave heating single node 120 °C, 2 x 5 min., and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 → 4:1) to give the title compound in 30% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.88 - 7.80 (m, 2H), 7.77 (d, J = 8.9 Hz, 1H), 7.58 (s, 1H), 7.55 (dd, J = 1.4, 9.1 Hz, 1H), 7.37 - 7.27 (m, 4H), 7.14 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 9.2 Hz, 1H), 4.70 (q, J = 6.9 Hz, 1H), 3.64 - 3.52 (m, 2H), 3.03 - 2.97 (m, 1H), 2.91 - 2.85 (m, 1H), 1.98 (octet, J = 6.7 Hz, 2H), 1.65 (d, J = 6.6 Hz, 3H).

Example 18

N-[(3, 4-Dichlorophenyl)methyl]-N'-(2-quinolinyl)-1, 3-cyclohexanediamine

This compound was prepared from N-quinolin-2-ylcyclohexane-1, 4-diamine and 3, 4-dichlorobenzaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a diastereomeric mixture in 66% yield. ^{1}H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.79 (d, J = 8.9 Hz, 1H), 7.60 - 7.53 (m, 3H), 7.50 - 7.45 (m, 2H), 7.31 (dd, J = 2.0, 10.1 Hz, 1H), 7.18 - 7.14 (m, 1H), 6.70 (d, J = 9.2 Hz, 1H), 4.04 - 3.96 (m, 1H), 3.89 (s, 2H), 2.88 - 2.81 (m, 1H), 2.47 (d, J = 12.1 Hz, 1H), 2.06 (d, J = 12.1 Hz, 2H), 1.92 - 1.86 (m, 1H), 1.80 - 1.67 (m, 1H), 1.54 - 1.42 (m, 1H), 1.29 - 1.12 (m, 2H).

Example 19

N-(9, 10-Methanoanthracen-9(10*H*)-ylmethyl)-N'-methyl-N'-(2-quinolinyl)-1, 3-propanediamine.

The title compound was isolated from synthesis of Example 14 . ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.90 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 7.27 - 7.23 (m, 3H), 7.15 - 7.10 (m, 3H), 7.02 (d, J = 8.8 Hz, 1H), 6.94 - 6.86 (m, 4H), 4.26

(s, 1H), 3.87 (t, J = 6.9 Hz, 2H), 3.63 (s, 2H), 3.18 (s, 3H), 2.85 (t, J = 6.6 Hz, 2H), 2.49 (s, 2H), 2.01 (quintet, J = 7.0 Hz, 2H).

Example 20

N-(2-Quinolinyl)-N'-(2-thienylmethyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 2-thiophenecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 18% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.84 (d, J = 8.9 Hz, 1H), 7.60 (dd, J = 1.7, 9.3 Hz, 1H), 7.47 - 7.42 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.20 - 7.17 (m, 1H), 7.10 (d, J = 3.2 Hz, 1H), 7.00 (dd, J = 3.7, 8.4 Hz, 1H), 6.74 (d, J = 9.4 Hz, 1H), 4.28 (s, 2H), 3.61 (t, J = 6.5 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 2.00 (quintet, J = 6.8 Hz, 2H).

Example 21

N-(3-Furanylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 3-furaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN $\rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 21% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 9.5 Hz, 1H), 7.54 (d, J = 6.8 Hz, 2H), 7.50 - 7.41 (m, 2H), 7.21 (t, J = 8.1 Hz, 1H), 6.75 (d, J = 9.1 Hz, 1H), 6.46 (t, J = 0.9 Hz, 1H), 4.04 (s, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.02 (t, J = 6.7 Hz, 2H), 2.03 (quintet, J = 6.6 Hz, 2H).

Example 22

N-[(3, 4-Dichlorophenyl)methyl]-N-methyl-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-methyl-N'-quinolin-2-ylpropane-1, 3-diamine and 3, 4-dichlorobenzaldehyde, and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 $\rightarrow$ 4:1) to give the title compound in 20% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.79 (d, J = 9.3 Hz, 1H), 7.60 - 7.55 (m, 2H), 7.49 - 7.44 (m, 2H), 7.33 (d, J = 9.3 Hz, 1H), 7.22 - 7.13 (m, 2H), 6.68

(d, J = 8.8 Hz, 1H), 3.49 (t, J = 7.4 Hz, 2H), 3.49 (s, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.22 (s, 3H), 1.87 (quintet, J = 7.2 Hz, 2H).

Example 23

N-[1-(9, 10-Methanoanthracen-9(10H)-ylmethyl)-4-piperidinyl]-2-quinolinamine

This compound was prepared from N-piperidin-4-ylquinolin-2-amine and 9-formyl-9,10-dihydro-9,10-methanoanthracene , and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 53% yield. ^{1}H NMR (400 MHz, THF-d_8) δ 7.77 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 9.1 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.47 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 6.6 Hz, 4H), 7.15 (t, J = 8.0 Hz, 1H), 6.99 - 6.90 (m, 4H), 6.68 (d, J = 9.0 Hz, 1H), 4.30 (s, 1H), 4.22 - 4.15 (m, 1H), 3.51 (s, 2H), 3.12 (d, J = 11.9 Hz, 2H), 2.63 (s, 2H), 2.52 (dt, J = 2.6, 12.6 Hz, 2H), 2.14 (d, J = 13.2 Hz, 2H), 1.59 (dq, J = 4.4, 12.7 Hz, 2H).

Example 24

N-(1H-Indol-3-ylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and indole-3-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 19% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.83 (d, J = 8.9 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.19 - 7.13 (m, 3H), 7.06 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 9.4 Hz, 1H), 4.41 (s, 2H), 3.66 (t, J = 6.1 Hz, 2H), 3.10 (t, J = 6.7 Hz, 2H), 2.06 (quintet, J = 6.6 Hz, 2H).

Example 25

N-(2-Naphthylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 2-naphthaldehyde, but the reaction was performed at room temperature (no microwave

heating single node) using $NaBH_3CN$, and purified on SiO_2 (CH_2Cl_2:MeOH 40:1 → 10:1, containing 1% HOAc) to give the title compound in 73% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.91 - 7.87 (m, 4H), 7.80 - 7.77 (m, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.56 - 7.50 (m, 3H), 7.27 - 7.16 (m, 3H), 6.79 (d, J = 9.1 Hz, 1H), 4.38 (s, 2H), 3.68 (t, J = 6.3 Hz, 2H), 3.18 (t, J = 7.2 Hz, 2H), 2.12 (quintet, J = 6.6 Hz, 2H).

Example 26

N-(2, 2-Diphenylethyl)-N´-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and diphenyl-acetaldehyde, but the reaction was performed at room temperature (no microwave heating single node) using $NaBH_3CN$, and purified on SiO_2 (CH_2Cl_2:MeOH 30:1 → 10:1, containing 1% HOAc) to give the title compound in 53% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J = 9.1 Hz, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.34 - 7.19 (m, 12H), 6.73 (d, J = 8.9 Hz, 1H), 4.32 (t, J = 8.0 Hz, 1H), 3.75 (d, J = 8.0 Hz, 2H), 3.58 (t, J = 6.2 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 2.05 - 1.98 (m, 2H).

Example 27

N-(1H-Indol-3-ylmethyl)-N´-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine

This compound was prepared from *N*-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and indole-3-carboxaldehyde, and purified using HPLC (95% 0.1 M ammoniumacetatebuffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 22% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.60 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.31 (s, 1H), 7.18 - 7.02 (m, 4H), 6.96 (dd, J = 2.7, 12.0 Hz, 1H), 6.61 (s, 1H), 4.38 (s, 2H), 3.84 (s, 3H), 3.61 (t, J = 5.8 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 2.50 (d, J = 0.8 Hz, 3H), 2.04 (quintet, J = 6.5 Hz, 2H).

Example 28

N-[(3, 4-Dichlorophenyl)methyl-*N*'-(2-quinolinyl)-1, 3-propanediamine**

This compound was prepared from *N*-quinolin-2-yl-1, 3-propanediamine and 3, 4-dichloro-benzaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 44% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.82 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.44 - 7.41 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.24 (dd, J = 2.5, 10.5 Hz, 1H), 7.19 - 7.15 (m, 1H), 6.72 (d, J = 8.9 Hz, 1H), 3.92 (s, 2H), 3.59 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.96 (quintet, J = 6.7 Hz, 2H).

Example 29

***N*-[(3, 4-Dichlorophenyl)methyl]-*N*'-(2-quinolinyl)-1, 4-cyclohexanediamine**

This compound was prepared from *N*-quinolin-2-ylcyclohexane-1, 4-diamine and 3, 4-dichlorobenzaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a mixture of isomers in 45% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.84 (d, J = 9.1 Hz, 1H), 7.65 - 7.46 (m, 5H), 7.35 (dd, J = 2.0, 10.3 Hz, 1H), 7.20 - 7.15 (m, 1H), 6.82 (d, J = 9.1 Hz, 1H), 4.20 - 4.16 (m, 1H), 3.95 (s, 2H), 2.92 - 2.85 (m, 1H), 2.22 - 2.16 (m, 1H), 2.02 - 1.98 (m, 2H), 1.89 - 1.84 (m, 2H), 1.79 - 1.67 (m, 3H).

Example 30

***N*, *N*'-Di-(2-quinolinyl)-1 ,3-propanediamine**

The title compound was isolated in 3% yield from synthesis of 2-quinolinyl-1, 3-propanediamine . ^1H NMR (400 MHz, MeOH-d_4) δ 7.77 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.9 Hz, 2H), 7.55 (m, 4H), 7.20 (t, J = 7.8 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 3.59 (bs, 4H), 1.92 (bt, J = 5.7 Hz, 2H).

Example 31

N-(2-Quinolinyl)-N'-(2-quinolinylmethyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 2-quinoline-carboxaldehyde, and purified on SiO_2 (EtOAc:MeOH 1:0 → 0:1) to give the title compound in 27% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.23 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.74 - 7.70 (m, 1H), 7.58 - 7.47 (m, 4H), 7.33 (t, J = 8.5 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 4.13 (s, 2H), 3.60 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.9 Hz, 2H), 1.96 (quintet, J = 6.7 Hz, 2H).

Example 32

N-[(1-Acetyl-1H-indol-3-yl)methyl]-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 1-acetyl-3-indolecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 25% yield. ^{1}H NMR (400 MHz, acetone-d_6, major rotamer) δ 7.77 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.61 (s, 1H), 7.57 (dd, J = 9.3, 1.4 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.28 (s, 1H), 7.10 (d, J = 8.9 Hz, 2H), 7.02 - 6.98 (m, 1H), 6.69 (d, J = 8.9 Hz, 1H), 4.01 (s, 2H), 3.64 - 3.61 (m, 2H), 2.86 - 2.81 (m, 2H), 2.53 (s, 3H), 1.90 - 1.86 (m, 2H).

Example 33

N-(Cyclopropylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and cyclopropanecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 17% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.07 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 6.4 Hz,

2H), 7.65 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.67 (t, J = 6.6 Hz, 2H), 3.16 (t, J = 7.3 Hz, 2H), 2.93 (d, J = 7.5 Hz, 2H), 2.10 (quintet, J = 7.3 Hz, 2H), 1.12 - 1.02 (m, 1H), 0.71 - 0.67 (m, 2H), 0.40 - 0.37 (m, 2H).

<u>Example 34</u>

N-(2-Quinolinyl)-N'-(3-thienylmethyl)-1, 4-cyclohexanediamine

This compound was prepared from N-quinolin-2-ylcyclohexane-1, 4-diamine and 3-thiophenecarboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound as a diastereomeric mixture in 27% yield. ^1H NMR (400 MHz, MeOH-d_4, major isomer) δ 7.78 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.55 (dd, J = 9.3, 1.2 Hz, 1H), 7.45 (t, J = 8.5 Hz, 1H), 7.35 (dd, J = 7.9, 3.0 Hz, 1H), 7.26 - 7.24 (m, 1H), 7.16 - 7.10 (m, 2H), 6.78 (d, J = 9.1 Hz, 1H), 4.18 - 4.16 (m, 1H), 3.81 (s, 2H), 2.65 (septet, J = 4.1 Hz, 1H), 1.92 - 1.83 (m, 2H), 1.80 - 1.64 (m, 5H), 1.64 - 1.54 (m, 1H).

<u>Example 35</u>

N-([1, 1'-Biphenyl]-4-ylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 4-biphenylcarboxaldehyde, but the reaction was performed at room temperature (no microwave heating single node) using $NaBH_3CN$, and purified on SiO_2 (CH_2Cl_2:MeOH 30:1 $\rightarrow$ 10:1, containing 1% HOAc) to give the title compound in 46% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.84 (d, J = 9.2 Hz, 1H), 7.62 – 7.56(m, 5H), 7.48 – 7.40 (m, 5H), 7.36 (t, J = 7.1 Hz, 1H), 7.23 (d, J = 8.5Hz, 1H), 7.16 (t, J = 8.5 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H),

4.21 (s, 2H), 3.66 (t, J = 5.8 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 2.07 (m, 2H).

Example 36

N-(6-Methoxy-4-methyl-2-quinolinyl)-N'-[3-(5-methyl-2-furanyl)butyl]-1, 3-propanediamine

This compound was prepared from N-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and 3-(5-methyl-2-furyl)butyraldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 46% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.54 (d, J = 8.9 Hz, 1H), 7.22 (dd, J = 2.6, 8.7 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 6.72 (d, J = 1.0 Hz, 1H), 5.96 - 5.94 (m, 2H), 3.92 (s, 3H), 3.56 (t, J = 6.6 Hz, 2H), 2.93 - 2.88 (m, 2H), 2.77 - 2.75 (m, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.53 (d, J = 0.8 Hz, 3H), 2.25 (d, J = 0.8 Hz, 3H), 1.90 - 1.82 (m, 2H), 1.72 - 1.67 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H).

Example 37

N-[[4-(Dimethylamino)phenyl]methyl]-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 4-dimethylaminobenzaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 22% yield. ^1H NMR (400 MHz, MeOH-d_4) δ 7.85 (d, J = 9.0 Hz, 1H), 7.60 (dd, J = 1.5, 9.4 Hz, 1H), 7.39 (t, J = 8.5 Hz, 1H), 7.24 - 7.17 (m, 4H), 6.74 (d, J = 9.1 Hz, 1H), 6.70 (d, J = 9.0 Hz, 2H), 4.07 (s, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.04 (t, J = 6.6 Hz, 2H), 2.94 (s, 6H), 2.05 (quintet, J = 6.6 Hz, 2H).

Example 38

N-(1H-Pyrrol-2-ylmethyl)-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and pyrrole-2-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 61% yield. ^1H

NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J = 9.3 Hz, 1H), 7.61 (dd, J = 1.7, 9.8 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.22 - 7.18 (m, 2H), 6.81 (dd, J = 1.5, 4.3 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 6.22 (dd, J = 1.8, 5.0 Hz, 1H), 6.13 (t, J = 3.2 Hz, 1H), 4.18 (s, 2H), 3.66 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 2.04 (quintet, J = 6.5 Hz, 2H).

Example 39

N-[3-(5-Methyl-2-furanyl)butyl]-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 3-(5-methyl-2-furyl)-butyraldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 19% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 1.2, 9.3 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.53 - 7.49 (m, 2H), 7.24 - 7.20 (m, 1H), 6.76 (d, J = 9.1 Hz, 1H), 5.86 (d, J = 3.0 Hz, 2H), 5.84 - 5.83 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.92 - 2.75 (m, 4H), 2.18 (d, J = 0.8 Hz, 3H), 1.98 (quintet, J = 6.6 Hz, 3H), 1.90 (s, 3H), 1.87 - 1.78 (m, 4H).

Example 40

N-[(5-Nitro-3-thienyl)methyl]-N'-(2-quinolinyl)-1, 3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 5-nitrothiophene-3-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 15 min 25 ml/min.) to give the title compound in 64% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.94 (d, J = 1.7 Hz, 1H), 7.87 (d, J = 9.1 Hz, 1H), 7.78 (d, J = 1.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 4.11 (s, 2H), 3.64 (t, J = 6.6 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 2.04 (quintet, J = 6.6 Hz, 2H).

Example 41

N-(6-Methoxy-4-methyl-2-quinolinyl)-N'-[(5-nitro-3-thienyl)methyl]-1, 3-propanediamine

This compound was prepared from N-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and 5-nitrothiophene-3-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 63% yield. ^1H NMR (400 MHz, DMF-d_7) δ 8.09 (d, J = 1.8 Hz, 1H), 7.87 - 7.87 (m, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 2.8, 11.7 Hz, 1H), 6.67 (d, J = 1.0 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 2H), 3.54 (t, J = 6.6 Hz, 2H), 2.70 (t, J = 6.7 Hz, 2H), 2.49 (d, J = 1.0 Hz, 3H), 1.82 (quintet, J = 6.7 Hz, 2H).

Example 42

N-(6-Methoxy-4-methyl-2-quinolinyl)-N'-(1H-pyrrol-2-ylmethyl)-1, 3-propanediamine

This compound was prepared from N-(6-methoxy-4-methyl-2-quinolinyl)-1, 3-propanediamine and pyrrole-2-carboxaldehyde, and purified using HPLC (95% 0.1 M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 min 25 ml/min.) to give the title compound in 83% yield. ^1H NMR (400 MHz, DMF-d_7) δ 7.56 (d, J = 8.9 Hz, 1H), 7.36 (d, J = 2.8 Hz, 1H), 7.31 (dd, J = 3.0, 11.9 Hz, 1H), 6.95 - 6.93 (m, 1H), 6.86 (d, J = 0.8 Hz, 1H), 6.19 - 6.17 (m, 1H), 6.15 - 6.13 (m, 1H), 4.13 (s, 2H), 4.05 (s, 3H), 3.71 (t, J = 6.5 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.66 (d, J = 0.8 Hz, 3H), 2.11 - 2.10 (m, 2H).

Example 43

N-[(3,4-Dichlorophenyl)methyl]-N'-methyl-N'-2-quinolinyl)-1, 3-propanediamine

The title compound was isolated from the synthesis of Example 22. ^1H NMR (400 MHz, MeOH-d_4) δ 7.93 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.45 - 7.37 (m, 3H), 7.32 (d, J = 8.3 Hz, 1H), 7.18 - 7.14 (m, 1H), 7.09 (dd, J = 2.0, 10.3 Hz, 1H), 6.99 (d, J = 9.3

Hz, 1H), 3.83 (t, J = 6.7 Hz, 2H), 3.65 (s, 2H), 3.12 (s, 3H), 2.58 (t, J = 6.7 Hz, 2H), 1.91 (quintet, J = 7.0 Hz, 2H).

Example 44

N-[1-(2,5-Dimethyl-3-thienyl)ethyl]-N'-(2-quinolinyl)-1,3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 3-acetyl-2, 5-dimethylthiophene, but subjected to microwave heating single node 120 °C, 10 min., and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 → 4:1) to give the title compound in 26% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.84 (d, J = 9.1 Hz, 1H), 7.61 (dd, J = 1.7, 9.7 Hz, 1H), 7.49 - 7.45 (m, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.72 (d, J = 9.4 Hz, 1H), 6.43 (s, 1H), 4.40 (q, J = 6.9 Hz, 1H), 3.71 - 3.55 (m, 2H), 2.99 - 2.83 (m, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 2.06 - 1.95 (m, 2H), 1.91 (s, 3H).

Example 45

N-[1-(2,5-Dichloro-thiophen-3-yl)-ethyl]-N'-(2-quinolinyl)-1,3-propanediamine

This compound was prepared from N-quinolin-2-yl-1, 3-propanediamine and 1-(2,5-dichloro-thiophen-3-yl)-ethanone, but subjected to microwave heating single node 120 °C, 5 min., and purified on SiO_2 (CH_2Cl_2:MeOH 10:0 → 4:1) to give the title compound in 11% yield. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.79 (d, J = 8.8 Hz, 1H), 7.56 (bt, J = 8.0 Hz, 2H), 7.49 - 7.44 (m, 1H), 7.16 (dt, J = 1.2, 7.4 Hz, 1H), 6.70 (s, 1H), 6.69 (bd, J = 9.0 Hz, 1H), 3.93 (q, J = 6.7 Hz, 1H), 3.59 (m, 1H), 3.47 (m, 1H), 2.50 (m, 2H), 1.81 (m, 2H), 1.28 (d, J = 6.9 Hz, 3H).

Example 46

N-[(1-acetyl-1H-indol-3-yl)methyl]-N'-quinolin-2-ylcyclohexane-1,3-diamine

A solution of N-quinolin-2-ylcyclohexane-1,3-diamine (1.01 mmol, 0.243 g) and 1-acetyl-1H-indole-3-carboxaldehyde (0.63 mmol, 0.118 g) in MeOH:CH_2Cl_2 (1:2, containing 1% HOAc, 9 mL) was stirred at ambient temperature for 1 h, after which a solution of $NaBH_3CN$ (2.50 mmol, 0.16 g) in MeOH (1.5 mL) was added. The reaction mixture was stirred at room temperature until LC/MS indicated that starting material was consumed. Methanol (10 mL) was added and the reaction mixture was concentrated. The residue was

purified on SiO_2 eluted with CH_2Cl_2:MeOH (95:5) and finally CH_2Cl_2:MeOH (9:1) to give 0.095 g (37%) of the title compound as a diastereomeric mixture (approx. 3:1). ^1H NMR (400 MHz, MeOH-d_4) δ 8.36 (d, J = 8.1 Hz, 1H, major isomer), 8.32 (d, J = 8.3 Hz, 1H, minor isomer), 7.77 (d, J = 8.9 Hz, 1H), 7.63-7.12 (m, 8H), 6.73 (d, J = 8.9 Hz, 1H, minor isomer), 6.69 (d, J = 8.9 Hz, 1H, major isomer), 4.42 (m, 1H, minor isomer), 4.06-3.96 (m, 1H, major isomer), 3.97 (s, 2H, major isomer), 3.96 (s, 2H, minor isomer), 3.00 (m, 1H, minor isomer), 2.82 (tt, J = 11.2, 3.6 Hz, 1H, major isomer), 2.60 (s, 3H, major isomer), 2.50-2.42 (m, 1H), 2.46 (s, 3H, minor isomer), 2.14-1.09 (m, 7H) . ^{13}C NMR (75 MHz, DMSO-d_6) δ (mixture of isomers) 168.4, 156.0, 148.0, 137.4, 137.2, 136.0, 129.8, 129.4, 127.3, 125.9, 125.3, 123.5, 123.2, 122.7, 121.8, 121.5, 119.0, 118.8, 116.7, 111.6, 111.0, 55.4, 52.3, 48.5, 46.0, 42.0, 41.8, 39.5, 32.7, 32.6, 31.7, 23.9, 22.1, 19.9.
LC-MS $[M+H]^+$ 413

Example 47

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclopentane-1,3-diamine

a) *tert*-butyl {(1*S*,3*S*)-3-[(6-methoxy-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate

A mixture of 2-chloro-6-methoxy-4-methylquinoline (3.33 mmol, 0.690 g), *tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate (5.0 mmol, 1.00 g), NaO^{t}Bu (4.66 mmol, 0.45 g), $Pd(OAc)_2$ (0.33 mmol, 0.075 g), and BINAP (0.33 mmol, 0.207 g) in toluene (30 mL) was stirred at 100 °C under nitrogen until LC/MS indicated that starting material was consumed. The reaction mixture was cooled to room temperature, poured into Et_2O (300 mL) and washed with brine. The organic layer was then separated, dried over Na_2SO_4 and evaporated to dryness. The residue was purified on a SiO_2 column eluted with CH_2Cl_2:MeOH (95:5) to give 0.618 g (50%) of the title compound.
LC-MS $[M+2H]^+$ 373

b) (1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

Tert-butyl {(1*S*,3*S*)-3-[(6-methoxy-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate (1.48 mmol, 0.550 g) and TFA (3 mL) in $CHCl_3$ (7 mL) was stirred at rt. for 6 hours. LC

indicated that starting material was consumed. The mixture was then evaporated to dryness. pH was set to 10 with a 2 *N* NaOH solution and then extracted with EtOAc. The organic layer was separated, dried on $MgSO_4$ and concentrated, to give 0.400 g (99%) of the title compound. ^{1}H NMR (300 MHz, CDCl3) δ 7.57 (d, 1H), 7.16-7.20 (dd 1H), 7.04 (d, 1H), 6.51 (s, 1H), 5.24 (br, 1H), 4.44 (m, 1H), 3.86 (s, 3H), 3.50 (m, 1H), 2.73 (br, 2H), 2.51 (s, 3H), 2.26 (m, 2H), 2.06 (m, 1H), 1.85 (m, 1H), 1.41 (m, 2H).

c) (1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine (0.74 mmol, 0.200 g) and thiophene-3-carboxylaldehyde (0.74 mmol, 0.083 g) in MeOH:CH_2Cl_2 (1:1, containing 1% HOAc, 5 mL) was stirred at ambient temperature for 1 h, after which a solution of $NaBH_3CN$ (1.48 mmol, 0.093 g) in MeOH (1 mL) was added. The reaction mixture was stirred at room temperature until LC-MS indicated that starting material was consumed. Methanol (5 mL) was added and the reaction mixture was concentrated. The residue was dissolved in MeCN and filtrated. The filtrate was then evaporated to dryness, dissolved in MeCN (10 mL) and purified by prep. HPLC (H_2O:MeCN) to give 0.180 g (95%) of the title compound. ^{1}H NMR (300 MHz, CDCl3) δ 7.58 (d, 1H), 7.27-7.29 (m, 1H), 7.19-7.23 (dd , 1H), 7.13 (d, 1H), 7.04-7.08 (m, 2H), 6.53 (s, 1H), 4.75 (br, 1 H), 4.38 (m, 1H), 3.89 (s, 3H), 3.80 (s, 2H), 3.33-3.38 (m, 1H), 2.54 (s, 3H), 2.31 (m, 1H), 1.95-2.08 (m, 2H), 1.85 (m, 1H), 1.49-1.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.6, 155.1, 144.9, 141.7, 128.0, 127.8, 126.2, 124.2, 122.0, 120.7, 111.4, 104.0, 57.7, 56.0, 52.3, 47.9, 41.2, 32.9, 32.2, 19.6.

MS (ESI) 368 ($M + H^+$).

__Example 48__

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine (0.74 mmol, 0.200 g) and 1-Methyl indole-3-carboxyaldehyde (0.74 mmol, 0.118 g) in MeOH:CH_2Cl_2 (1:1, containing 1% HOAc, 5 mL) was stirred at ambient temperature for 1 h, after which a

solution of $NaBH_3CN$ (1.48 mmol, 0.093 g) in MeOH (1 mL) was added. The reaction mixture was stirred at room temperature until LC-MS indicated that starting material was consumed. Methanol (5 mL) was added and the reaction mixture was concentrated. The residue was dissolved in MeCN and filtrated. The filtrate was then evaporated to dryness, dissolved in MeCN (10 mL) and purified by prep. HPLC (H_2O:MeCN) to give 0.050 g (16%) of the title compound. ^{1}H NMR (300 MHz, CDCl3) δ 7.61-7.68 (m, 2H), 7.25-7.30 (m, 3H), 7.10-7.15 (m, 2H), 7.03 (s, 1H), 6.56 (s, 1H), 4.90 (br, 1H), 4.40-4.44 (q, 1 H), 3.98 (s, 2H), 3.81 (s, 3H), 3.48 (s, 3H), 3.44-3.48 (m, 1H), 2.56 (s, 3H), 2.31-2.35 (m, 1H), 2.02-2.10 (m, 2H), 1.84-1.91 (m, 1H), 1.54-1.60 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.4, 154.8, 144.6, 143.0, 137.2, 127.6, 127.5, 123.9, 121.8, 120.4, 119.1, 118.9, 113.2, 111.0, 109.4, 103.7, 57.4, 55.7, 52.1, 43.2, 40.8, 32.7, 32.6, 31.8, 19.3.
LC-MS $[M+H]^+$ 415.

<u>Example 49</u>

N-[(1-acetyl-1H-indol-3-yl)methyl]-N'-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine

To a stirred solution of *N*-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (0.526 mmol, 0.150 g) and 1-acetyl-1*H*-indole-3-carbaldehyde (0.53 mmol, 0.098 g) in CH_2Cl_2/MeOH 2:1 containing 1% HOAc (5 mL), sodium cyanoborohydride (0.89 mmol, 0.056 g) was added. After 24 h, the mixture was concentrated and purified by flash chromatography, to give 0.119 g (50%) of the major diastereomer of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.1 Hz, 1H), 7.61-7.57 (m, 2H), 7.37-7.26 (m, 3H), 7.19 (dd, J = 9.1, 2.8 Hz, 1H), 7.06 (d, J = 12.8 Hz, 1H), 6.42 (s, 1H), 4.88 (br, 1H), 4.04-3.95 (m, 3H), 3.86 (s, 3H), 2.82 (m, 1H), 2.58 (s, 3H), 2.48 (s, 3H), 2.44-2.38 (m, 1H), 2.11-1.82 (m, 4H), 1.52-1.11 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 155.0, 154.7, 144.0, 143.5, 136.2, 130.0, 127.9, 125.4, 124.1, 123.7, 122.7, 121.9, 120.0, 119.0, 116.8, 112.1, 103.8, 55.7 (2C), 48.7, 42.1, 40.1, 33.1, 32.8, 24.1, 22.4, 19.1; LC-MS $[M+H]^+$ 457.3.

A minor diastereomer was isolated and further purified by HPLC (95% 0.1M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 mL/min) to give 0.027 g (11%) of the minor diastereomer of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (bs, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.37-7.25 (m, 3H), 7.18 (d, J = 8.3 Hz,

1H), 7.07 (s, 1H), 6.50 (s, 1H), 4.69 (bs, 1H), 4.29 (bs, 1H), 4.01 (d, J = 13.6 Hz, 1H), 3.96 (d, J = 13.6 Hz, 1H), 3.88 (s, 3H), 3.03 (bs, 1H), 2.53 (s, 3H), 2.52 (s, 3H), 1.92-1.4 (m, 9H); LC-MS $[M+H]^+$ 457.3.

Example 50

N-(1H-indol-3-ylmethyl)-N'-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine

The title compound was isolated from synthesis of Example 49 and further purified by HPLC (95% 0.1M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 mL/min) to give 0.013 g (6%) of the title compound as a single diastereomer. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.62 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.26 (s, 1H), 7.17-7.09 (m, 3H), 7.06 (m, 1H), 6.57 (s, 1H), 4.05 (s, 2H), 3.92 (tt, J = 11.4, 3.8 Hz, 1H), 3.86 (s, 3H), 2.86 (tt, J = 11.3, 3.7 Hz, 1H), 2.49 (s, 3H), 2.47-2.41 (m, 1H), 2.08-2.02 (m, 1H), 1.90-1.82 (m, 1H), 1.52-1.40 (m, 1H), 1.24-1.11 (m, 3H); LC-MS $[M+H]^+$ 415.3.

Example 51

N-(6-methoxy-4-methylquinolin-2-yl)-N'-(3-thienylmethyl)cyclohexane-1,3-diamine

N-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (0.16 mmol, 0.046 g) in CH_2Cl_2/MeOH 1:1 (1.2 mL), thiophene-3-carboxaldehyde (0.12 mmol, 0.014 g) in CH_2Cl_2 (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (150 mg, pre-swollen in CH_2Cl_2, 0.6 mL). The resultant slurry was subjected to microwave heating single node 100 °C, 5 min. The resin was filtered and washed with portions (1-2 mL) of CH_2Cl_2 and MeOH, and the filtrate was concentrated. The residue was purified on HPLC (95% 0.1M ammonium acetate buffer:5% $CH_3CN \rightarrow$ 100% CH_3CN, 10 mL/min) to give 0.021 g (39%) of the title compound as a mixture of diastereomers (~5:1). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.56 (m, 1H, minor isomer), 7.55 (d, J = 9.1 Hz, 1H, major isomer), 7.44-7.40 (m, 2H), 7.33 (dd, J = 5.0, 3.0 Hz, 1H, minor isomer), 7.25 (m, 1H, minor isomer), 7.19-7.13 (m, 3H) 7.07 (dd, J = 5.0, 1.2 Hz, 1H, minor isomer), 6.66 (bs, 1H, minor isomer), 6.59 (bs, 1H, major isomer), 4.36 (m, 1H, minor isomer), 4.02 (s, 2H, major isomer), 4.01 (s, 2H, minor isomer), 3.94 (tt, J = 11.5, 3.7 Hz, 1H, major isomer), 3.87 (s, 3H, minor isomer), 3.86 (s, 3H, major isomer), 3.10 (m, 1H, minor isomer), 2.94 (tt, J =

11.6, 3.7 Hz, 1H, major isomer), 2.52-2.46 (m, 1H, major isomer), 2.52 (s, 3H, minor isomer), 2.50 (s, 3H, major isomer), 2.34-2.28 (m, 1H, minor isomer), 2.12-1.15 (m, 7H); ^{13}C NMR (101 MHz, MeOH-d_4, major isomer) δ 156.6, 156.2, 145.7, 143.7, 137.9, 129.0, 127.5, 127.3, 125.4, 125.2, 120.9, 114.3, 104.9, 56.3, 56.0, 49.3, 45.1, 38.9, 33.6, 31.4, 23.9, 18.9; LC-MS $[M+H]^+$ 382.2.

<u>Example 52</u>

N-(6-methoxy-4-methylquinolin-2-yl)-N'-[(1-methyl-1H-indol-3-yl)methyl]cyclohexane-1,3-diamine

N-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (0.16 mmol, 0.046 g) in CH_2Cl_2/MeOH 1:1 (1.2 mL), 1-methylindole-3-carboxaldehyde (0.13 mmol, 0.021 g) in CH_2Cl_2 (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (150 mg, pre-swollen in CH_2Cl_2, 0.6 mL). The resultant slurry was subjected to microwave heating single node 100 °C, 10 min. The resin was filtered and washed with portions (1-2 mL) of CH_2Cl_2 and MeOH, and the filtrate was concentrated. The residue was purified on HPLC (95% 0.1M ammonium acetate buffer:5% CH_3CN → 100% CH_3CN, 10 mL/min) to give 0.021 g (34%) of the title compound as a mixture of diastereomers (~6:1). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.65 (d, J = 8.1 Hz, 1H, major isomer), 7.59-7.55 (m, 1H, minor isomer), 7.54 (d, J = 9.1 Hz, 1H, major isomer), 7.37 (d, J = 8.3 Hz, 1H, major isomer), 7.30 (d, J = 8.3 Hz, 1H, minor isomer), 7.27 (s, 1H, major isomer), 7.23-7.07 (m, 5H), 7.01-6.97 (m, 1H, minor isomer), 6.62 (s, 1H, minor isomer), 6.58 (s, 1H, major isomer), 4.36 (m, 1H, minor isomer), 4.20 (s, 2H), 3.95 (tt, J = 11.4, 3.7 Hz, 1H, major isomer), 3.87 (s, 3H, minor isomer), 3.85 (s, 3H, major isomer), 3.78 (s, 3H, major isomer), 3.59 (s, 3H, minor isomer), 3.21 (m, 1H, minor isomer), 3.07 (tt, J = 11.5, 3.4 Hz, 1H, major isomer), 2.58-2.40 (m, 1H), 2.51 (s, 3H, minor isomer), 2.49 (s, 3H, major isomer), 2.18-1.19 (m, 7H); LC-MS $[M+H]^+$ 429.3.

Example 53

N-(1-benzofuran-2-ylmethyl)-N'-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine

N-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (0.14 mmol, 0.040 g) in CH_2Cl_2/MeOH 1:1 (1.2 mL), benzofuran-2-carboxaldehyde (0.13 mmol, 0.018 g) in CH_2Cl_2 (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (150 mg, pre-swollen in CH_2Cl_2, 0.6 mL). The resultant slurry was subjected to microwave heating single node 100 °C, 10 min. The resin was filtered and washed with portions (1-2 mL) of CH_2Cl_2 and MeOH, and the filtrate was concentrated. The residue was purified on a Biotage Horizon 25 mm silica column (linear gradient EtOAc/MeOH 19:1, containing 1% NEt_3 → EtOAc/MeOH 1:1, containing 1% NEt_3, 10 mL/min) to give 0.015 g (26%) of the title compound as a mixture of diastereomers (~10:1). ^1H NMR (400 MHz, MeOH-d_4) δ 7.54-7.10 (m, 7H), 6.68 (s, 1H, major isomer), 6.61 (s, 1H, minor isomer), 6.57 (s, 1H, major isomer), 6.47 (s, 1H, minor isomer), 4.31 (m, 1H, minor isomer), 3.95 (s, 2H), 3.95-3.85 (m, 1H, major isomer), 3.85 (s, 3H), 2.89 (m, 1H, minor isomer), 2.72 (tt, J = 11.2, 3.6 Hz, 1H, major isomer), 2.48 (s, 3H), 2.40-2.34 (m, 1H), 2.06-1.05 (m, 7H); LC-MS $[M+H]^+$ 416.2.

Example 54

N-(6-methoxy-4-methylquinolin-2-yl)-N'-(pyridin-2-ylmethyl)cyclohexane-1,3-diamine

N-(6-methoxy-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (0.14 mmol, 0.040 g) in CH_2Cl_2/MeOH 1:1 (1.2 mL), pyridin-2-carboxaldehyde (0.13 mmol, 0.014 g) in CH_2Cl_2 (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (150 mg, pre-swollen in CH_2Cl_2, 0.6 mL). The resultant slurry was subjected to microwave heating single node 100 °C, 10 min. The resin was filtered and washed with portions (1-2 mL) of CH_2Cl_2 and MeOH, and the filtrate was concentrated. The residue was purified on a Biotage Horizon 25 mm silica column (linear gradient EtOAc/MeOH 19:1, containing 1% NEt_3 → EtOAc/MeOH 1:1, containing 1% NEt_3, 10 mL/min) to give 0.015 g (45%) of the title compound as a mixture of diastereomers (~10:1). ^1H NMR (400 MHz, MeOH-d_4) δ 8.49 (m, 1H, major isomer), 8.42 (m, 1H, minor isomer), 7.78 (td, J = 7.7, 1.8 Hz, 1H, major

isomer), 7.65 (td, $J = 7.7$, 1.8 Hz, 1H, minor isomer), 7.52 (d, $J = 9.1$ Hz, 1H, major isomer), 7.44 (d, $J = 7.9$ Hz, 1H, major isomer), 7.37 (d, $J = 7.9$ Hz, 1H, minor isomer), 7.30-7.27 (m, 1H), 7.23-7.08 (m, 2H), 6.64 (bs, 1H, minor isomer), 6.57 (bs, 1H, major isomer), 4.36 (m, 1H, minor isomer), 3.95-3.87 (m, 1H, major isomer), 3.92 (s, 2H), 3.86 (s, 3H, minor isomer), 3.85 (s, 3H, major isomer), 3.29 (m, 1H, minor isomer), 2.69 (tt, $J =$ 11.2, 3.7 Hz, 1H, major isomer), 2.50 (s, 3H, minor isomer), 2.49 (s, 3H, major isomer), 2.40-2.32 (m, 1H), 2.08-1.98 (m, 2H), 1.88-1.07 (m, 5H); LC-MS $[M+H]^+$ 377.2.

Example 55

***N*-(4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine**

N-(4-methylquinolin-2-yl)cyclohexane-1,3-diamine (75 mg, 0.29 mmol) in 2 mL of CH_2Cl_2/MeOH 1:1, and 3-thiophenaldehyde (26 mg, 0.23 mmol) in 1 mL of CH_2Cl_2, and 0.10 mL of acetic acid were added to Pol-BH_3CN (0.25 g, preswollen in 1 mL of CH_2Cl_2). The resultant slurry was subjected to single node microwave heating (100°C for 10 min). The resin was filtered and washed with 1-2 mL portions of CH_2Cl_2 and MeOH. The filtrates were combined and poured onto a 1 g SCX-2 prepacked ion-exchange column, washed with 10 mL of MeOH and the product was eluted with MeOH containing 10% of Et_3N. The purity was not satisfactory and the product was further purified on a Biotage Horizon 12 mm silica column (linear gradient EtOAc/MeOH 9:1 → EtOAc/MeOH 1:1, 10 mL/min) to give 20 mg (19%) of the title compound as a mixture of diastereomers (~3:1). ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.68-7.75 (m, 1H), 7.5-7.6 (m, 1H), 7.0-7.5 (m, 5H), 6.61 (bs, 1H, minor isomer), 6.54 (bs, 1H, major isomer), 4.36 (m, 1H, minor isomer), 4.11 (s, 2H, major isomer), 4.09 (s, 2H, minor isomer), 3.95 (m, 1H, major isomer), 3.09 (m, 1H, major isomer; minor isomer obscured under the MeOH-d_4 signal), 2.35-2.6 (m, 4H; thereof 2.48, 3H, minor isomer, and 2.46, 3H, major isomer), 1.1-2.2 (m, 7H).

^{13}C NMR (75 MHz, MeOH-d_4, major isomer) δ 179.4, 157.3, 148.0, 146.7, 134.7, 130.4, 128.9, 128.0, 127.0, 125.6, 124.8, 123.0, 113.9, 68.1, 56.4, 44.2, 37.5, 33.1, 30.2, 23.8, 18.8.

LC-MS $[M+H]^+$ 352.3.

APPENDIX

Names/reference numbers of starting materials

Commercial starting material (CAS no): 2-chloroquinoline, 612-62-4; 2-chloro-6-methoxy-4-methylquinoline, 6340-55-2; 1,3-diaminopropane, 109-76-2; ethylenediamine, 107-15-3; 1, 3-cyclohexanediamine, 3385-21-5; 1, 4- cyclohexanediamine, 3114-70-3; 4-aminopiperidine, 13035-19-3; *N*-methyl-1, 3-propanediamine, 6291-84-5; 3-thiophenecarboxaldehyde, 498-62-4; 3-acetylthiophene, 1468-83-3; 4-keto-4, 5, 6 ,7-tetrahydrothianaphthene, 13414-95-4; 3-acetylthianaphthene, 1128-05-8; 2-thiophenecarboxaldehyde, 98-03-3; 5-nitrothiophene-3-carboxaldehyde, 75428-45-4; 3-acetyl-2,5-dimethylthiophene, 2530-10-01; 1-acetyl-3-indolecarboxaldehyde, 22948-94-3; indole-3-carboxaldehyde, 487-89-8; pyrrole-2- carboxaldehyde, 1003-29-8; 2, 4, 6-trimethyl-benzaldehyde, 487-68-3; phenylacetaldehyde, 122-78-1; 3, 4-dichlorobenzaldehyde, 6287-38-3; 2-naphthaldehyde, 66-99-9; 2-quinolinecarboxaldehyde, 5470-96-2; diphenylacetaldehyde, 947-91-1; 4-biphenylcarboxaldehyde, 3218-36-8; 4-dimethylaminobenzaldehyde, 100-10-7; 3-furaldehyde, 498-60-2; 3-(5-methyl-2-furyl)butyraldehyde, 31704-80-0; cyclopropanecarboxaldehyde, 1489-69-6; 1-methylindole-3-carboxaldehyde, 19012-03-4; benzofuran-2-carboxaldehyde, 4265-16-1; pyridin-2-carboxaldehyde, 1121-60-4 3-acetyl-2,5-dichlorothiophene, 36157-40-1; (-)-2-azabicyclo[2.2.1]hept-5-en-3-one,79200-56-9 and 2-chloro-4-methylquinoline 634-47-9

Pharmacological Properties

MCH1 receptor radioligand binding.

Assays were performed on membranes prepared from HEK293 cells stably expressing the human Melanin concentrating hormone receptor 1 (MCH1r) (Lembo et al. Nature Cell Biol 1 267-271). Assays were performed in a 96-well plate format in a final reaction volume of 200μl per well. Each well contained 6,1μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per

minute) per well. Each well contained 2μl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at room temperature for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1μM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).

Non-specific binding was subtracted from all values determined. Maximum binding was that determined in the absence of any competitor following subtraction of the value determined for non-specific binding. Binding of compounds at various concentrations was plotted according to the equation

y = A+((B-A)/1+((C/x)^D)))

and IC_{50} estimated where

A is the bottom plateau of the curve i.e. the final minimum y value
B is the top of the plateau of the curve i.e. the final maximum y value
C is the x value at the middle of the curve. This represents the log EC50 value when A + B = 100
D is the slope factor.
x is the original known x values.
y is the original known y values.

The compounds exemplified herein had an IC_{50} of less than 2 μmolar in the above assay. Preferred compounds had an activity of less than 1 μmolar. For Example the IC_{50}s of Examples 2, 29 and 53 were 0.01, 0.40 and 0.56 μmol, respectively.

Assays were also performed on membranes prepared from HEK293 cells stably expressing the rat Melanin concentrating hormone receptor 1 (MCH1r) (Lembo et al. Nature Cell Biol 1 267-271). Assays were performed in a 96-well plate format in a final reaction

volume of 200μl per well. Each well contained 5μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2μl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at room temperature for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1μM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).